Remarks

Claims 1-62, 68-75 and 82-87 are pending.

Rejections Under 35 U.S.C. § 103

1. Claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229; Lizardi '229) in view of Schweitzer et al. (PNAS 2000). Applicants respectfully traverse this rejection.

In order for a reference or a combination of references to make obvious a claim or claims, "[f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

Lizardi '229 discloses compositions and a method for detecting single nucleic acid molecules using rolling circle amplification (RCA) of amplification target circles (ATC), primed by immobilized primers. In one form of the method, referred to as bipartite primer rolling circle amplification (BP-RCA), RCA of the ATC depends on the formation of a primer by target-mediated ligation. In BP-RCA a probe and a combination probe/primer oligonucleotide can hybridize to adjacent sites on a target sequence in the presence of a nucleic acid molecule having the target sequence, thus allowing the probes to be ligated together. The ligated primer can then be used to prime replication of its cognate ATC. As acknowledged in the Office Action on page 6, lines 20-21, Lizardi '229 fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid.

Schweitzer et al. discloses a method of detecting protein antigens referred to as "immunoRCA". In immunoRCA, an oligonucleotide primer is covalently attached to an antibody at its 5' end. In the presence of circular DNA, DNA polymerase, and nucleotides, the oligonucleotide primes amplification of the circular DNA. The passages cited in the Office Action fail to disclose or suggest use of a capture tag to associate cDNA with a rolling circle

replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid

Furthermore, the passages of Schweitzer et al. cited in the Office Action fail to disclose or refer specifically to RT primers. The passages of Schweitzer et al. cited in the Office Action also fail to disclose RT primers that comprise a capture tag or use of such a capture tag to associate a rolling circle replication primer with cDNA. The passages of Schweitzer et al. cited in the Office Action also fail to disclose RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle.

(a) Arguments For Claims 1-15, 18-29, 56-58, 61, 68, 71, 73, 82 and 87

(i) In the method of claims 1-15, 18-29, 56-58, 61, 68, 71, 73, 82 and 87, cDNA produced from mRNA is associated with rolling circle replication primers, where the rolling circle replication primers (claims 1-15, 18-29, 68, 82 and 87) or the cDNA (claims 56-58, 61, 71, 73) comprise a capture tag, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, where the capture tag is not a nucleic acid, and where the association between the rolling circle replication primer and cDNA occurs via the capture tag. That is, the claims require that either the rolling circle replication primer comprises a capture tag or the cDNA comprises a capture tag and that the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody and not a nucleic acid. The claims further require that the association between the rolling circle replication primers and cDNA occurs via the capture tag (see step (c) of claim 1; step (c) of claim 56, lines 6-8 of claim 68; lines 6-8 of claim 71; step (c) of claim 73; and step (c) of claim 87).

The Office Action alleges (page 3, lines 7-9) that Lizardi '229 teaches "mixing one or more rolling circle replication primers with the cDNA strands under conditions that promote association of the cDNA strands with the rolling circle replication primers, wherein the rolling circle replication primers". The Office Action does not allege nor provide any support that Lizardi '229 teaches or suggests association between the rolling circle replication primers and cDNA that occurs via a capture tag. Furthermore, as noted above the Office Action admits on page 6, lines 20-21, that Lizardi '229 fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand

binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid.

Schweitzer et al. was cited for allegedly disclosing a capture tag that is an antibody. Applicant's first note that the Office Action does not cite Schweitzer et al. for teaching the subject matter of claim 1. The Office Action only cites Schweitzer et al. against claims 2, 39, 40, 42, 45, 54, 57, 55 and 58. The Office Action fails to provide any evidence of how Schweitzer et al. in combination with Lizardi '229 teaches all the elements of claims 1 (from which claims 2-15, 18-29 and 82 depend), 56 (from which claims 57-58 and 61 depend), 68, 71, 73 71, 73, or 87. Specifically, the Office Action fails to provide any evidence that either Schweitzer et al. or Lizardi '229 teach or suggest association of a rolling circle replication primer and cDNA that occurs via a capture tag. As such, the Examiner has not met her burden of providing evidence that the art teaches each of the elements of all the claims

Applicants further submit that neither Lizardi '229 nor Schweitzer et al., either alone or in combination disclose an association between a rolling circle replication primer and cDNA that occurs via a capture tag. With regard to Lizardi '229, the Office Action cites column 42, lines 27-52 of Lizardi '229, which describes formation of a rolling circle replication primer by target-mediated ligation of two oligonucleotides: a half probe and a probe/primer. In the cited passage of Lizardi '229 the half probe and a portion of the probe/primer hybridize to a target DNA molecule via base pairing. Thus, association of the primer and the target DNA molecule in Lizardi '229 occurs by a nucleotide to nucleotide base pairing interaction between the sequences of the target DNA molecule and of the half probe and probe/primer. In contrast, in the currently pending claims, the capture tag is not a nucleic acid. As such, the nucleotide to nucleotide base pairing interaction between the sequences of the target DNA molecule and of the half probe and probe/primer does not meet the current claim requirements of a capture tag.

With regard to Schweitzer et al., the Office Action cites the abstract for teaching a capture tag associating with a primer for use in the immunoRCA method. While it is true that the abstract of Schweitzer et al. does disclose the attachment of an oligonucleotide primer to an antibody, the claims require more. As described above, the "association" referred to in the claims refers to the association of the cDNA strands (produced from a reverse transcription reaction) and the rolling circle replication primers. Specifically, the claims require that the

association between the rolling circle replication primer and cDNA occurs via the capture tag. At best, Schweitzer et al. teaches a primer associated with a capture tag. The Office Action failed to cite any evidence of where Schweitzer et al. provides any teaching, motivation, or suggestion, to associate a rolling circle replication primer with cDNA (produced from the reverse transcription reaction) via a capture tag. Schweitzer et al. merely discloses using an oligonucleotide primer associated with an antibody to detect proteins. Nowhere, in Schweitzer et al. is there any mention of associating a rolling circle replication primer with cDNA, nor is there any mention of amplifying messenger RNA.

The Office Action does allege on page 7, line 22 – page 8, line 2 that an ordinary practitioner would have been motivated to use the method of attaching an antibody capture tag to a primer, as taught by Schweitzer et al. with the method of amplifying target nucleic acids as taught by Lizardi '229 in order to expand the genus of analytes which can be detected using RCA. First, Applicants note that the claims are not drawn to an "expanded genus of analytes". The claims are drawn to methods of amplifying and using messenger RNA. The motivation to expand the genus of analytes which can be detected using RCA is not the subject matter claimed in the current application. Furthermore, the Office Action fails to provide any evidence within the four corners of the cited references that support the allegation that one of skill in the art would be motivated to combine the references to reach the currently claimed subject matter. The Office Action has also failed to provide where either reference provides a teaching or suggestion to combine the two references to achieve the claimed subject matter. This does not satisfy the Examiner's burden of providing evidence of a teaching, motivation or suggestion present in either Lizardi '229 or the Schweitzer et al. reference to combine the oligonucleotide primer-antibody of Schweitzer et al. with the method of Lizardi '229 to achieve the currently claimed subject matter.

The cited prior art must provide a description of every element of the claimed method and provide a suggestion or motivation to combine the prior art to arrive at the claimed method. The cited publications both fail to disclose every element of the claimed method (association of a rolling circle replication primer and cDNA that occurs via a capture tag, for example) and any suggestion or motivation to combine such (non-existent) elements to arrive at the claimed method. As it stands, the present rejection merely refers to irrelevant aspects of both Lizardi

'229 and Schweitzer et al. No rationale for combination of these disparate elements is provided and none is apparent. Applicants note in particular that it has not been established, nor is it apparent, how or why one of skill in the art would think that the oligonucleotide/antibody molecule of Schweitzer et al. could or should be used in the BP-RCA method of Lizardi '229 This does not meet the burden of the Patent Office to establish a prima facie case of obviousness. For at least these additional reasons, claims 1-15, 18-29, 56-58, 61, 68, 71, 73, 82 and 87 are not obvious in view of the cited publications.

Because the rejection clearly fails to provide any evidence, reasoning or rationale that could possibly support the present rejection, and because such failure constitutes a failure to establish a prima facie case of obviousness, Applicants note that the present rejection should be withdrawn.

B. Arguments For Claims 53-55, 70, and 86

In the method of claims 53-55, 70, and 86, cDNA produced from mRNA is associated with rolling circle replication primers, where the RT primers used to produce the cDNA comprise capture tags, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. That is, the claims require use of an RT primer that comprises a capture tag that is the basis for the association of the rolling circle replication primers and the cDNA.

The cited passage of Lizardi '229 fails to disclose or refer specifically to RT primers, fails to disclose RT primers that comprise a capture tag, and fails to disclose use of such a capture tag to associate a rolling circle replication primer with cDNA. The Office Action mailed June 15, 2006 alleged (page 3, lines 1-4) that Lizardi '229 teaches "mixing one or more RT primers with a nucleic acid sample and reverse transcribing to produce cDNA strands each comprising one of the RT primers, wherein each RT primer comprises a reverse transcription primer portion." For support, the Office Action cited column 77, line 2 of Lizardi '229, which merely mentions use of cDNA produced by reverse transcription. The passage does not mention any primers used to produce cDNA, does not describe any features of such primers, and does not describe the use of such primers. Thus, the cited passage of Lizardi '229 fails to disclose or refer specifically to RT primers, fails to disclose RT primer that comprise a capture tag, and fails to disclose use of such a capture tag to associate a rolling circle replication primer with cDNA.

The Office Action attempts to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed (see Office Action page 3, lines 3-4). The Office Action appears to make the leap that because RNA can be used, RT primers are automatically disclosed.

The Office Action also attempts to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed therein and that Lizardi '229 teaches cDNA which inherently requires the use of RT primers (see Office Action page 11, lines 3-7). The Office Action further alleges that a practitioner of ordinary skill in the art recognizes the need for using RT primers when working with RNA and moreover, primers are primers (see Office Action page 11, lines 5-8). The Office Action alleges that RT primers (primers for producing cDNA) are not structurally different from DNA primers (primers for producing DNA). The Office Action then makes the leap that because the combination of Lizardi '229 and Schweitzer et al. allegedly render the instant invention obvious with respect to DNA primers then it necessarily renders the instant invention obvious with respect to RT primers (see Office Action page 2, lines 9-11).

First, Applicants respectfully submit that even if RNA can be used in the methods of Lizardi '229 and even if the use of RNA in the methods of Lizardi et al requires RT primers, the currently claimed RT primers are not "just" primers. The currently claimed RT primers comprise special components, capture tags, that "all" primers do not just have. Although, it may be true that general RT primers and DNA primers are generally similar, the currently claimed RT primers are not simply primers. Even assuming for the sake of argument that RT primers are inherent in Lizardi '229, the Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise capture tags wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid, and that the association between the rolling circle replication primers and cDNA occurs via the capture tags.

Schweitzer et al. fails to supplement the elements missing from Lizardi '229. Schweitzer et al. was cited for allegedly disclosing a capture tag that is an antibody. Specifically, the Office Action on page 6, lines 23-24 alleges that Schweitzer et al. teaches the capture tag associates with the primer. In support of its allegation, the Office Action cites the abstract for teaching

"where the primer is covalently attached to the antibody". "The primer" referred to in the abstract is a rolling circle replication primer and not an RT primer. In fact, since Schweitzer et al. is concerned with the detection of proteins, an RT primer would have no use. Nowhere, in Schweitzer et al. is there any mention of RT primers, nor is there any sort of teaching, motivation, or suggestion to replace the rolling circle replication primer in Schweitzer et al. with an RT primer.

As such, Schweitzer et al., like Lizardi '229, fails to disclose RT primers that comprise a capture tag wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid. The Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise a capture tag wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid and that the association between the rolling circle replication primers and cDNA occurs via the capture tags.

Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claims 53-55 and 70. Accordingly, and for all of the above reasons, Lizardi '229 and Schweitzer et al. fail to make obvious claims 53-55, 70, and 86. Applicants respectfully request withdrawal of this rejection.

C. Arguments for Claims 62 and 72

The method of claims 62 and 72 requires the use of RT primers that comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. That is, the claims require use of an RT primer that comprises a rolling circle replication primer portion that is the basis for the association of the rolling circle replication primers with amplification target circles.

The cited passage of Lizardi '229 fails to disclose RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. The Office Action alleges (page 3, lines 1-4) that Lizardi '229 teaches "mixing one or more RT primers with a nucleic acid sample and reverse transcribing to produce cDNA strands

each comprising one of the RT primers, wherein each RT primer comprises a reverse transcription primer portion." For support, the Office Action cites column 77, line 2 of Lizardi '229, which merely mentions use of cDNA produced by reverse transcription. The passage does not mention any primers used to produce cDNA, does not describe any features of such primers, and does not describe the use of such primers. Thus, the cited passage of Lizardi '229 fails to disclose or refer specifically to RT primers, fails to disclose RT primers that comprise a rolling circle replication primer portion, and fails to disclose use of such an RT primer to associate the rolling circle replication primer portion with an amplification target circle.

The Office Action attempts to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed therein and that Lizardi '229 teaches cDNA which inherently requires the use of RT primers (see Office Action page 11, lines 3-7). The Office Action further alleges that a practitioner of ordinary skill in the art recognizes the need for using RT primers when working with RNA and moreover, primers are primers (see Office Action page 11, lines 5-8). The Office Action alleges that RT primers (primers for producing cDNA) are not structurally different from DNA primers (primers dor producing DNA). The Office Action then makes the leap that because the combination of Lizardi '229 and Schweitzer et al. allegedly render the instant invention obvious with respect to DNA primers then it necessarily renders the instant invention obvious with respect to RT primers (see Office Action page 2, lines 9-11).

Schweitzer et al. fails to supplement the elements missing from Lizardi '229 Schweitzer et al. was cited for allegedly disclosing a capture tag that is an antibody. However, Schweitzer et al. fails to disclose RT primers that comprise a rolling circle replication primer portion, and fail to disclose use of such an RT primer to associate the rolling circle replication primer portion with an amplification target circle. Specifically, the Office Action on page 6, lines 23-24 alleges that Schweitzer et al. teaches the capture tag associates with the primer. In support of its allegation, the Office Action cites the abstract for teaching "where the primer is covalently attached to the antibody". "The primer" referred to in the abstract is a rolling circle replication primer and not an RT primer. In fact, since Schweitzer et al. is concerned with the detection of proteins, an RT primer would have no use. Nowhere, in Schweitzer et al. is there any mention of RT primers,

nor is there any sort of teaching, motivation, or suggestion to replace the rolling circle replication primer in Schweitzer et al. with an RT primer.

Again, Applicants respectfully submit that the claimed RT primers are not "just" primers. The currently claimed RT primers comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. Although, it may be true that general RT primers and DNA primers are generally similar, the currently claimed RT primers are not simply primers. The claimed RT primers are specifically designed to contain sequences that serve as a basis for association with a specific ATC. Even assuming for the sake of argument that RT primers are inherent in Lizardi '229, the Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle.

Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claims 62 and 72. Accordingly, and for all of the above reasons, Lizardi '229 and Schweitzer et al. fail to make obvious claims 62 and 72. Applicants respectfully request withdrawal of this rejection.

D. Arguments for Claims 37-39

The method of claims 37-39 also requires the use of RT primers that comprise a capture tag. The cited passage of Lizardi '229 fails to disclose or refer to RT primers that comprise a capture tag. The Office Action alleges (page 6, lines 13-14) that Lizardi '229 teaches "the RT primer comprises a capture tag" and that Lizardi '229 teaches "the biotin." For support, the Office Action cites column 23, lines 50-67 of Lizardi '229, which discloses detection labels for nucleic acid amplified using rolling circle amplification and rolling circle transcription (see column 23, lines 18-23). The labels disclosed in the cited passage of Lizardi '229 are to be incorporated into or associated with amplified nucleic acids. This is not the same as what is presently claimed.

The method of claims 37-39 requires the use of RT primers that comprise a capture tag. Furthermore, the present method uses the claimed RT primers to produce cDNA the presence of

which allows production of amplified nucleic acid. In other words, neither the claimed RT primers nor the claimed cDNA produced with the RT primers are equivalent to the amplified nucleic acid referred to in column 23 of Lizardi '229 Furthermore, Lizardi '229 fails to disclose RT primers and cDNA that comprise the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Schweitzer et al. fails to supplement the elements missing from Lizardi '229 Schweitzer et al. was cited for allegedly disclosing the capture tag is an antibody. However, Schweitzer et al. fails to disclose or refer to RT primers and fails to disclose RT primers and cDNA that comprise the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Once again, Office Action attempts to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed therein and that Lizardi '229 teaches cDNA which inherently requires the use of RT primers (see Office Action page 11, lines 3-7). The Office Action further alleges that a practitioner of ordinary skill in the art recognizes the need for using RT primers when working with RNA and moreover, primers are primers (see Office Action page 11, lines 5-8). The Office Action alleges that RT primers (primers for producing cDNA) are not structurally different from DNA primers (primers dor producing DNA). The Office Action then makes the leap that because the combination of Lizardi '229 and Schweitzer et al. allegedly render the instant invention obvious with respect to DNA primers then it necessarily renders the instant invention obvious with respect to RT primers (see Office Action page 2, lines 9-11).

Applicants again respectfully submit that even if RNA can be used in the methods of Lizardi '229 and even if the use of RNA in the methods of Lizardi et al requires RT primers, the currently claimed RT primers are not "just" primers. The currently claimed RT primers comprise special components, capture tags, that "all" primers do not just have. Although, it may be true that general RT primers and DNA primers are generally similar, the currently claimed RT primers are not simply primers. In addition, the currently claimed RT primers comprise a capture tag that comprises labels such as biotin, digoxigenin, bromodeoxyuridine, and other haptens. Even assuming RT primers are inherent in Lizardi '229, the Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA

comprise capture tags in general, much less RT primers that specifically comprise a capture tag that comprises labels such as biotin, digoxigenin, bromodeoxyuridine, and other haptens.

Thus, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claims 37-39. Accordingly, Lizardi '229 and Schweitzer et al. do not make obvious claims 37-39. Applicants therefore respectfully requests withdrawal of this rejection.

E. Additional Arguments for Claims 39-41

The method of claims 39-41 also requires the use of cDNA that comprises a capture tag. The cited passage of Lizardi '229 fails to disclose cDNA that comprises a capture tag. The Office Action allege (page 6, line 15) that Lizardi '229 teaches "the biotin." It is unclear what the Examiner intended this to mean, as the claims require more than just "the biotin". For support, the Office Action cited column 23, lines 50-67 of Lizardi '229, which discloses labels in tandem sequence DNA (TS-DNA; which is the product of rolling circle amplification). The labels disclosed in the cited passage of Lizardi '229 are to be incorporated into or associated with amplified nucleic acids (TS-DNA). This is not the same as what is presently claimed.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid referred to in column 23 of Lizardi '229. The cDNA of the claimed method serves as the template to which the rolling circle replication primer associates, wherein the association occurs via the capture tag. The general assertion made in the Office Action that Lizardi '229 discloses RNA and further discloses cDNA fails to account for these differences. Lizardi '229 fails to disclose or refer to cDNA that comprises the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Again, Schweitzer et al. fails to supplement the elements missing from Lizardi '229 Schweitzer et al. was cited for allegedly disclosing a capture tag that is an antibody. The Office Action on page 7, lines 1-2 cites Schweitzer et al. for allegedly teaching "the DNA strands comprise capture tags". For support, the Office Action cites the abstract of Schweitzer et al., which discloses an oligonucleotide primer covalently attached to an antibody (see abstract, lines 3-4). Nothing in the abstract, nor anywhere else in Schweitzer et al. is there any mention of cDNA that comprises a capture tag. Furthermore, nowhere in Schweitzer et al. is there any

mention of incorporating a capture tag into cDNA produced from RNA. Schweitzer et al. fails to disclose or refer to cDNA and fails to disclose or refer to cDNA that comprises the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Thus, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claims 39-41. Accordingly, Lizardi '229 and Schweitzer et al. do not make obvious claims 39-41. Applicants therefore respectfully request withdrawal of this rejection.

F. Arguments for Claim 46 and 47

Applicants first note that the Office Action alleges on page 2, lines 20-22 that claim 47 is unpatentable over Lizardi '229 in view of Schweitzer et al. However, the Office Action fails to specifically address claim 47 in the following pages. Nowhere in the Office Action is there any further mention of claim 47. As such, Applicants respectfully submit that this does not satisfy the Examiner's burden of providing evidence of a teaching, motivation or suggestion present in either Lizardi '229 or Schweitzer et al. of each limitation of each claim. However, in the interest of being thorough, Applicants will address claim 47's patentability.

The method of claims 46 and 47 requires the use of cDNA that comprises a capture tag. The cited passage of Lizardi '229 fails to disclose cDNA that comprises a capture tag. The Office Action alleged (page 6, line 15) that Lizardi '229 teaches teaches "the biotin." It is unclear what the Examiner intended this to mean, as the claims require more than just "the biotin". For support, the Office Action cited column 23, lines 50-67 of Lizardi '229, which discloses labels in tandem sequence DNA (TS-DNA; which is the product of rolling circle amplification). The labels disclosed in the cited passage of Lizardi '229 are to be incorporated into or associated with amplified nucleic acids (TS-DNA). This is not the same as what is presently claimed.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid (TS-DNA) referred to in column 23 of Lizardi '229. Lizardi '229 fails to disclose or refer to cDNA and fails to disclose cDNA that comprises biotin.

Schweitzer et al. fails to supplement the elements missing from Lizardi '229 Schweitzer et al. was cited for allegedly disclosing a capture tag that is an antibody. However, Schweitzer

et al. fails to disclose or refer to cDNA and fails to disclose cDNA that comprises biotin. The Office Action provides no evidence of where Schweitzer et al. teaches any such moity.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid referred to in column 23 of Lizardi '229 The cDNA of the claimed method serves as the template to which the rolling circle replication primer associates, wherein the association occurs via the capture tag. In claims 46 and 47, the cDNA comprises a capture tag of biotin and a rolling circle replication primer comprising a capture tag that is an antibody that binds biotin, respectfully. The general assertion made in the Office Action that Lizardi '229 discloses RNA and further discloses cDNA fails to account for these differences. Lizardi '229 fails to disclose or refer to cDNA with a capture tag, fails to disclose or refer to cDNA that comprises biotin and fails to refer to a rolling circle replication primer that comprises and antibody that binds biotin.

Thus, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claims 46 and 47. Accordingly, Lizardi '229 and Schweitzer et al. do not make obvious claims 46 and 47. Applicants therefore respectfully request withdrawal of this rejection.

G. Arguments for Claims 83-85

Applicants first note that the Office Action alleges on page 2, lines 20-22 that claims 83-85 are unpatentable over Lizardi '229 in view of Schweitzer et al. However, the Office Action fails to specifically address claims 83-85 in the following pages. Nowhere in the Office Action is there any further mention of claims 83-85. Secondly, Applicants note that claims 83-85 depend from claim 48, which is not recited as being unpatentable over Lizardi '229 in view of Schweitzer et al. Consistent with the omission, claim 48 is not discussed under the rejection of Lizardi '229 in view of Schweitzer et al. Claim 48 is however cited on page 9, lines 15-17 as being unpatentable over Lizardi et al and Scweitzer et al. in view of Cao et al. However, claims 83-85 are not discussed under that rejection. The patentability of claim 48 is discussed below. As such, Applicants respectfully submit that this does not satisfy the Examiner's burden of providing evidence of a teaching, motivation or suggestion present in either Lizardi '229 or Schweitzer et al. of each limitation of each claim. Applicants therefore respectfully request withdrawal of this rejection.

For all of the above reasons, Lizardi '229 and Schweitzer et al fail to make obvious claims 1-15, 18-29, 53-58, 61, 62, 68, 70, 71, 72, 73, 82, 83-85, 86, 87.

2. Claims 16 and 17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) in view of Lizardi (US 2003/0032024 A1; Lizardi '024) Applicants respectfully traverse this rejection.

Applicants note that claims 16 and 17 depend from claim 1 and thus includes all of the limitations of claim 1. Applicants also note that the rejection applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claim 1. Specifically, Lizardi '229 and Schweitzer et al. either alone or in combination, fail to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags, and wherein the capture tag is not a nucleic acid.

Lizardi '024 fails to supplement the elements missing from Lizardi '229 and Schweitzer et al.. Lizardi '024 was cited for its disclosure of subprobes. Lizardi '024 fails to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. Thus, Lizardi '229, Schweitzer et al., and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claim 30. Accordingly, Lizardi '229, Schweitzer et al., and Lizardi '024do not make obvious claim 30. Applicants respectfully request withdrawal of this rejection.

3. Claim 30 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) and in further view of Waggoner et al. (U.S. Pat. No. 6,008,373). Applicants respectfully traverse this rejection.

Applicants note that claim 30 depends from claim 1 and thus includes all of the limitations of claim 1. Applicants also note that the rejection applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claim 1. Specifically, Lizardi '229 and Schweitzer et al. either alone or in combination, fail to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags, and wherein the capture tag is not a nucleic acid.

Waggoner et al. fails to supplement the elements missing from Lizardi '229 and Schweitzer et al.. Waggoner et al. was cited for its disclosure of using phycoerythrin as a fluorophore in the detection label on an antibody. Waggoner et al. fails to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. Thus, Lizardi '229, Schweitzer et al., and Waggoner et al., either alone or in combination, fail to disclose or suggest each and every element of claim 30. Accordingly, Lizardi '229, Schweitzer et al., and Waggoner et al. do not make obvious claim 30. Applicants respectfully request withdrawal of this rejection.

4. Claims 48-52, and 69 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) in view of Cao et al. (U.S. 2002/0120409). Applicants respectfully traverse this rejection.

With regard to claims 48-52, and 69 the Office Action applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 under 35 U.S.C. § 103(a) addressed above. As noted in the Office Action (page 9, lines 19-20) Lizardi '229 and Schweitzer et al. fail to teach fragmenting and labeling cDNA strands to

form labeled fragmented cDNA. Applicants submit that Lizardi '229 and Schweitzer et al. also fails to disclose or suggest adding a capture tag to the fragmented cDNA or associating a rolling circle replication primer with fragmented cDNA via a capture tag.

The cited passages of Cao et al. describe a method of fragmenting cDNA and incorporating a label into the cDNA, where the label can be biotin (see Cao et al. claim 1 and paragraphs 0045-0049). The incorporated label then serves as a means of detecting the labeled cDNA (see Cao et al., para. 49). Cao et al. does not disclose or suggest associating rolling circle replication primers with the fragmented cDNA via the labels or any other component. Thus, the label of Cao et al. is not a capture tag as claimed.

Claims 48-52 (as well as claims 83-85 which depend from claim 48 – see above) involve a method of amplifying messenger RNA, involving fragmenting cDNA strands to form fragmented cDNA, adding a capture tag to the fragmented cDNA, mixing the fragmented cDNA with a set of capture probes under conditions that promote hybridization of the fragmented cDNA to the capture probes, mixing one or more rolling circle replication primers with the fragmented cDNA under conditions that promote association of the fragmented cDNA with the rolling circle replication primers, where the association occurs via the capture tag. Thus the claims require adding a capture tag to the fragmented cDNA where a rolling circle replication primer associates with the fragmented cDNA via the capture tag.

Claim 69 involves a method of using messenger RNA, the method comprising replicating one or more amplification target circles to produce one or more tandem sequence DNAs, where each tandem sequence DNA is coupled to a rolling circle replication primer, where the rolling circle replication primer is associated with a fragmented cDNA strand, where the fragmented cDNA strand is hybridized to a capture probe, where the fragmented cDNA comprises a capture tag, where the association of the rolling circle replication primer and the fragmented cDNA strand occurs via the capture tag. Thus, like claims 48-52, claim 69 requires that the fragmented cDNA comprises a capture tag where the rolling circle replication primer associates with the fragmented cDNA strand via the capture tag of the cDNA strand.

None of Lizardi '229, Schweitzer et al. or Cao et al., either alone or in combination, disclose or suggest fragmented cDNA comprising a capture tag and association of a rolling circle replication primer with the fragmented cDNA via the capture tag. Therefore, the cited

publications fail to disclose or suggest every limitation of the present claims. Accordingly, the cited publications fail to make obvious claims 48-52, and 69.

5. Claims 59 and 60 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) in view of Shoemaker et al. (U.S. Pat. No. 6,713,257 B2). Applicants respectfully traverse this rejection.

Applicants note that claims 59 and 60 depend from claim 56 and thus include all the limitations of claim 56. Applicants also note that the rejection applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Schweitzer et al. fail to disclose or suggest every limitation of claims 59 and 60. Specifically, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags and wherein the capture tag is not a nucleic acid.

Shoemaker et al. fails to supplement the elements missing from Lizardi '229 and Schweitzer et al. Shoemaker et al. was cited for its disclosure of using an amino-allyl dUTP in labeling cDNA. Shoemaker et al. fails to disclose or suggest the use of a capture tag to associate cDNA with a rolling circle replication primer. Thus, Lizardi '229, Schweitzer et al., and Shoemaker et al., either alone or in combination, fail to disclose or suggest each and every element of claims 59 and 60. Accordingly, Lizardi '229, Schweitzer et al., and Shoemaker et al. do not make obvious claims 59 and 60. Applicants respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $60.00 for the fee for a small entity under 37 C.F.R. §1.17(a)(1) and a Request for One (1) Month Extension of Time are also enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Scott D. Marty, Ph.D.
Registration No. 53,277

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Scott D. Marty, Ph.D. — 9-29-06
Date